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The epigenetic regulation of centromeres and telomeres in plants and animals

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Abstract

The centromere is a chromosomal region where the kinetochore is formed, which is the attachment point of spindle fibers. Thus, it is responsible for the correct chromosome segregation during cell division. Telomeres protect chromosome ends against enzymatic degradation and fusions, and localize chromosomes in the cell nucleus. For this reason, centromeres and telomeres are parts of each linear chromosome that are necessary for their proper functioning. More and more research results show that the identity and functions of these chromosomal regions are epigenetically determined. Telomeres and centromeres are both usually described as highly condensed heterochromatin regions. However, the epigenetic nature of centromeres and telomeres is unique, as epigenetic modifications characteristic of both eu- and heterochromatin have been found in these areas. This specificity allows for the proper functioning of both regions, thereby affecting chromosome homeostasis. This review focuses on demonstrating the role of epigenetic mechanisms in the functioning of centromeres and telomeres in plants and animals.

Keywords

cytosine methylation, histone code, non-coding RNA, pericentromeric, subtelomeric

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Introduction

The term epigenetics refers to a variety of processes that change gene expression independently of DNA sequence. An important feature of the epigenetic pattern is that it is stable and inherited through cell divisions, although it can be reversible (John and Rougeulle 2018). Epigenetics is crucial for the proper development, differentiation and functioning of cells. The epigenome may change under the influence of various environmental conditions and stimuli from inside the cell (Shi et al. 2017). This epigenome diversity is provided by numerous epigenetic mechanisms, including DNA methylation, post-translational histone modifications, chromatin remodeling, histone variants and ncRNA (non-coding RNA) interaction (Kabesch et al. 2010).

DNA methylation is of great importance among the epigenetic mechanisms that regulate gene expression in plants and animals. DNA methylation is associated with gene silencing (Kumar et al. 2018). Methylcytosine (5-mC) is the most common among the modified bases in the eukaryotic genome and is often referred to as the fifth DNA base. Methylation of cytosine in DNA involves the covalent attachment of a methyl group at position 5 of the cytosine pyrimidine ring (5-mC). Analysis of the DNA methylation profile of the human genome showed that mainly cytosines in CpG dinucleotides are modified. In plants, cytosine methylation in DNA occurs in the CHG sequential contexts (H = C, A, T) and asymmetrically in CHH (Zhang et al. 2008). Cytosine methylation in DNA is catalyzed by DNA methyltransferases. In mammalian cells, DNA methyltransferase (DNMT1) is responsible for maintaining the methylation pattern during replication, DNMT3A (DNA methyltransferase 3A) and DNMT3B (DNA methyltransferase 3B) for *de novo* methylation. In plants, MET1 (methyltransferase 1), DDM1 (decrease in DNA methylation 1), CMT1 (chromomethylase 1) and DRM2 (domain rearranged methyltransferase 2) DNA methyltransferases are necessary to maintain the correct methylation pattern (Ogrocká et al. 2014, Zhang et al. 2018).

Chromatin remodeling results from the action of ATP-dependent complexes that change the association of DNA with core histones and from modifications of histone proteins, affecting the availability of DNA (Kang et al. 2020). The remodeling complexes change the structure of chromatin by repositioning, evicting or restructuring the nucleosome. Some complexes are involved in the formation of condensed chromatin, others promote the binding of transcription factors to DNA. They are therefore involved in such important processes as DNA transcription and replication, DNA repair and DNA recombination (Clapier and Cairns 2009). Chromatin remodeling factors are involved in the development and differentiation of cells in plants and animals. Chromatin remodelers include several sub-families of ATP-dependent enzymes. Each of these subfamilies has a specific composition of domains and subunits that are involved in histone exchange, assembly and repositioning of nucleosomes (Kang et al. 2020).

Post-translational modifications of histone proteins are another important epigenetic mechanism. Histones (H2A, H2B, H3 and H4)$_2$ are the basic protein component of the nucleosome that forms the core around which a DNA strand of about 146 bp is wrapped (Luger et al. 1997). The N- or C-terminal tails of histones undergo

post-translational modifications. These modifications include arginine (R) methylation, methylation, acetylation, ubiquitination and sumoylation of lysine (K) as well as phosphorylation of serine (S) and threonine (T). The pattern of these modifications creates a histone code, which shows the transcription potential of this genomic region (Kabesch et al. 2010). Appropriate histone modifications are necessary for the proper course of such important cellular processes as: DNA repair, replication, mitosis, apoptosis and gametogenesis. Histones, through post-translational modifications, participate in the regulation of DNA packaging, affecting the availability of chromatin for transcription factors (Quina et al. 2006). Histone modifications can change the structure of chromatin by changing the physical properties of individual nucleosomes. This affects the interaction between the DNA molecule and histone and creates an open chromatin structure that is available for many protein factors, or a higher order chromatin structure that prevents these factors from binding. These modifications are strengthened by protein complexes that do not participate in chromatin modifications, but by influencing its remodeling, they are of great importance for the epigenetic gene regulation (Kim et al. 2012). An important role in regulating the structure of chromatin is also played by histone variants, which differ from canonical histones by the amino acid sequence. The presence of specific histone variants affects transcription regulation, chromosome segregation, DNA repair, cell cycle regulation and apoptosis (reviewed in Henikoff and Smith 2015).

Epigenetic regulators also include non-coding RNA (ncRNA). In epigenetic processes, the most important role among non-coding RNAs is played by those molecules that act in the RNAi (RNA interference) pathway and certain lncRNA (long non-coding RNAs, over 200 nt in length) (Kurokawa et al. 2009). Detailed studies of biogenesis and function of ncRNA have elucidated their activity at many levels, forming an integrated interacting network in the cell. They can regulate expression at both the gene and chromosome level (Amaral and Mattick 2008) and can act at transcriptional and post-transcriptional levels by interacting with promoters, enhancers or chromatin remodeling complexes (Kurokawa et al. 2009). However, their influence is not limited to the euchromatin, as exemplified by centromeric sequences, where ncRNAs are necessary for the assembly and proper functioning of both centromere and kinetochore (Bobkov et al. 2018).

Most of the presented epigenetic mechanisms are closely associated with each other to ensure stabilization and transmission of epigenetic patterns from cell to cell during cell divisions. They interact with each other in different ways. DNA methylation can promote changes in histone modification and vice versa. However, they can also change accidentally under the influence of stimuli coming from the internal and external environment (Kabesch et al. 2010). Epigenetic mechanisms do not act solely at the level of gene expression regulation. They also play a key role in maintaining genomic stability. They are involved in the regulation of centromeres, telomeres and silencing transposable elements (TE), which enables proper chromosome segregation, reduces excessive recombination between repetitive elements, and prevents TE transposition (Dupont et al. 2009).

However, there is a fairly close connection between epigenetic regulators and the spatial structure of the cell nucleus due to the fact that the organization of chromatin is

epigenetically determined. In turn, the organization of chromatin influence the spatial structure of the cell nucleus. Based on the studies of the nucleus of mammalian cells, chromatin was divided into following compartments A – euchromatin, B – facultative heterochromatin (Solovei et al. 2016) and C – pericentromeric constitutive heterochromatin (Falk et al. 2019). It was shown that attractions between heterochromatic regions play crucial role in separation of the active from inactive parts of the genome in the nucleus. Constitutive heterochromatin, enriched with tandem repetitive sequences and transposable elements, located in the centromeric, pericentromeric or subtelomeric areas is the most enigmatic fraction of chromatin. Most of the heterochromatic regions remains unassembled due to their enrichment with the tandem repetitive sequences. The majority of the assembled mammalian genomes contain a 3 Mb Golden Path Gap (GPG) empty region around each centromere. However, gradually, more and more data on the composition of the sequence of constitutive heterochromatin regions are becoming available (Ostromyshenskii et al. 2018). Constitutive heterochromatin turns out to be surprisingly heterogeneous, characterized by plasticity, and its epigenetic regulators depend on the genomic context in which it is present. Although constitutive heterochromatin is gene-poor, its role turns out to be very significant (Saksouk et al. 2015).

The epigenetic nature of both centromeric and telomeric regions is not clearly defined. This is because these are regions built from repetitive sequences, which makes it difficult to accurately show epigenetic modifications of centromeres and telomeres. This review focuses on demonstrating how epigenetic mechanisms affect the functioning of centromeric and telomeric regions, taking into account differences in plants and animals.

Centromere and pericentromere

The centromere was first described by Walther Flemming (1882), who observed that there was one region in the chromosome that was smaller in diameter than the remaining portion of the chromosome. Cytogenetic and molecular analyses demonstrated centromeres as heterochromatin chromosomal domains that control the formation of the kinetochore, a protein structure that interacts with the mitotic spindle, ensuring proper segregation of chromosomes (reviewed in Cleveland et al. 2003, Allshire and Karpen 2008, Salmon and Bloom 2017).

The simplest centromere with a length of 125 bp is found in *Saccharomyces cerevisiae* (Meyen, 1883). This simple, small centromere contains a single cenH3 (centromere specific histone 3) nucleosome, which binds a single microtubule during cell division, which is why this centromere type is called the "point centromere" (Pluta et al. 1995, Furuyama and Biggins 2007). Numerous studies have shown that not all eukaryotic organisms have monocentric chromosomes characterized by the presence of the primary constriction. In some species, microtubules of the mitotic spindle attach to the chromosome along its entire length (White 1973). Thus, two types of chromosomes are distinguished: monocentric chromosomes that connect to the microtubules of the

spindle in a single region, and holocentric chromosomes, characterized by the presence of dispersed kinetochores that bind to spindle microtubules over their entire length (Wrench et al. 1994, Mandrioli and Manicardi 2012).

Holocentric chromosomes have been found in some plants (e.g. the genus *Luzula* Candolle and Lamarck, 1805 *)*, animals (several arthopods and nematodes) and Rhizaria (Cavalier-Smith, 2002) (Allshire and Karpen 2008, Heckmann et al. 2013). It is believed that holocentromeres have been evolved from monocentromeres at least 13 times independently, and their organization varies among taxa (Melters et al. 2012). The type of DNA sequence responsible for the formation of dispersed centromeres is not yet fully elucidated. The sequences located in the holocentromeres are very diverse, including those that directly bind cenH3. In *Rhynchospora pubera* (Linnaeus, 1872) holocentromeres are enriched in specific satellite DNA sequences (Tyba) (which bind CENH3) and retrotransposons (Ribeiro et al. 2017). In *Caenorhabditis elegans* (Maupas, 1900) specific satDNA (satellite DNA) sequences that bind CENH3 are dispersed all over the genome (Subirana et al. 2018). In turn, no centromere-specific sequences were found in *Luzula elegans* (Lowe, 1838) (Heckmann et al. 2013). Hence, cenH3 probably binds not to specific sequences but to chromatin of appropriate status, indicating epigenetic regulation of holocentromers. The unusual structure of holokinetic chromosomes is also associated with the specific course of meiosis. Three types of meiosis can be distinguished in different species characterized by holocentric chromosomes: 'chromosome remodeling', 'functional monocentricity' and 'inverted chromatid segregation' (Heckmann et al. 2014, Lukhtanov et al. 2018). In *C. elegans* chromosome remodeling ensure chromosomes segregation typical for monocentric chromosomes. Other species have developed functional monocentricity, i.e. attachment of microtubules to one terminus of the chromosome, thus, holocentric chromosomes act as monocentric. These adaptations allow for a course of meiosis similar to canonical meiosis. In the first meiotic division, homologous chromosomes segregate, while sister chromatids are separated during the second meiotic division. However, many species with holokinetic chromosomes have developed an inverted meiosis, in which the order of major meiosis events is reversed, i.e. the sister chromatids are separated first (which results, among others, from the inability to maintain cohesion of sister chromatids up to AII (anaphase II) in holocentric chromosomes), followed by segregation of homologues (Heckmann et al. 2014, Lukhtanov et al. 2018).

In monocentric chromosomes of animals and plants the centromere region constitutes a segment from several kb to Mb in size, that contains satellite DNA with repeating monomers of ~100–400 bp (Melters et al. 2013). In general, chromosome centromeres in one species are characterized by the occurrence of a single family of sequence repeats (Zhong et al. 2002, Nagaki et al. 2003, Henikoff et al. 2015). This type of centromere restricted to a certain region is referred to as the regional centromere (Melters et al. 2013, Liu et al. 2015, Kursel and Malik 2016).

In plants, the centromeric region is composed of alternating tandem repeats and retrotransposons. For example, sequencing of maize centromeric DNA revealed two types of repetitive sequences in this region: satellite CentC (156 bp monomer) and

retrotransposon CRM (centromeric *retrotransposon* of maize) sequences (Ananiev et al. 1998, Zhong et al. 2002, Birchler and Han 2009). In B chromosome of maize, an additional sequence was identified in this region known as B-repeat (Alfenito and Birchler 1993), flanked and interspersed with typical maize centromeric sequences, i.e. CentC and CRM (Jin et al. 2005, Lamb et al. 2005). A similar organization of sequences is found in rice centromeres, where the CentO satellite repetitive sequence (155 bp monomer) as well as the CRR (centromeric retrotransposon of rice) retrotransposon sequence are distinguished (Cheng et al. 2002); other examples are pBV repetitive sequences and r retrotransposon of the beetle family in *Beta vulgaris* (Linnaeus, 1753) (Zakrzewski et al. 2013). A combination of satellite repeats in association with retrotransposons in the centromere region was also detected in *Hordeum* (Linnaeus, 1753) (Houben et al. 2007), *Saccharum officinarum* (Linnaeus, 1753) (Nagaki and Murata 2005), *Brassica* (Linnaeus, 1753) (Wang et al. 2011), *Raphanus sativus* (Linnaeus, 1753) (He et al. 2015) and *Glycine* (Linnaeus, 1753) (Tek et al. 2010).

Human centromeres are characterized by the presence of satellite tandem repeats of ~171 bp in size, arranged "head-to-tail", that are further arranged in higher order repeats (HOR). Individual monomers share 50–70% sequence identity, but HORs have 95–98% similarity (Warburton et al. 1996, Alcan et al. 2007). The functional core of the centromere is composed of highly homogeneous HORs, and, depending on the chromosome, spans a region from 0.5 to 5 Mb (Altemose et al. 2014), flanked by 500-kb segments, containing *L1* (*LINE1*, long interspersed nuclear *elements*) mobile elements (Schueler et al. 2001, Aldrup-MacDonald and Sullivan 2014). Within the human centromere, in the a satellite DNA sequences, 17-bp sequence motifs occur, referred to as the CENP-B box, which are recognized by centromere protein B (CENP-B) (Masumoto et al. 1993). This protein has an important role in maintaining stability and in the proper arrangement of centromere nucleosomes, because it binds with N-terminus of CENP-A (centromere protein A) and CENP-C (centromere protein C) (Fachinetti et al. 2015, Fujita et al. 2015). Human Y chromosome (Choo 2001) or neocentromeres (Fachinetti et al. 2015) are an exception, as the CENP-B box sequences and CENP-B proteins were not detected, while other centromeric proteins were present. It is known, however, that the lack of the CENP-B box in α-satellite sequences or mutations in these regions do not allow the formation of artificial chromosomes (Zhang et al. 2010). This suggests that CENP-B is not necessary for the centromere function, however, it contributes to its stabilization and maintenance (Schalch and Steiner 2017).

Centromeric DNA sequences are evolving relatively fast (Melters et al. 2013), which seems surprising considering the conservative function of the centromere (Henikoff et al. 2001, Rosin and Mellone 2017). Large differences in centromere sequences among wild *Oryza* species (Linnaeus, 1753) (Lee et al. 2005), cultivated *Canavalia* (Adanson, 1763) species (She et al. 2017), between related species of *Solanum tuberosum* (Linnaeus, 1753) and *S. verrucosum* (Schlechtendal, 1839) (Zhang et al. 2014), or within one species of *Pisum sativum* (Linnaeus, 1753) (Macas et al. 2007), can serve as examples. Hence, it is presumed that centromeres are not genetically determined by the occurrence of a specific DNA sequence, but they are rather epigenetically

defined by characteristic modifications (Simon et al. 2015). The confirmation of this fact are neocentromeres, which act as centromeres at the new chromosomal site even if satellite sequences are not present there (Williams et al. 1998, Marshall et al. 2008). Although satellite DNA is an inherent element of centromeres, it is not required for the functioning of these regions (Willard 1990, Csink and Henikoff 1998). Nevertheless, repeated DNA is the preferred DNA environment for centromere formation, and if the neocentromere is formed in a region devoid of repetitive sequences, then they begin to gradually accumulate there (Han et al. 2009, Plohl et al. 2014).

The centromeric core, which provides the kinetochore attachment site, is flanked by pericentromeric regions. Pericentromeric chromatin stabilizes the centromeric core, inhibiting internal recombination between core repeat sequences (Hetrr and Allis 2005), and is responsible for the attachment of sister chromatids during cell division (Schalch and Steiner 2017), promoting bidirectionality and creating tension between them (Bernard et al. 2001, Sakuno et al. 2009, Yamagishi et al. 2010, Yi et al. 2018).

Pericentromeres, like the core centromere, mainly consist of repetitive sequences. Among the sequences included in pericentromeric DNA, there are satellite sequences, as well as transposons, LTR and non-LTR retrotransposons (Smurova and Wulf 2018). Typically, these regions are described as genetically inactive, although some of the sequences found in these regions, such as 5S rRNA genes are highly transcribed (Cloix et al. 2002, Simon et al. 2015). Pericentromeric sequences show both inter- and intraspecific variation (Charlesworth et al. 1994, Plohl et al. 2008).

Epigenetic regulation of centromeres and pericentromeres

As previously mentioned, it is believed that satellite DNA is not essential for maintaining centromere structure and function. The term "centromere paradox" defines the fact that centromere sequences are very variable, while centromere function is conservatively maintained. However, as it turns out, centromere functionality does not result from the composition of the relevant DNA sequences, but the epigenetic mechanisms are responsible for it (Allshire and Karpen 2008). Epigenetic mechanisms play an important role in the establishment, maintenance and functioning of centromeres (Allshire and Karpen 2008) (Table 1). Centromere can be inactivated (Sullivan and Schwartz 1995, Han et al. 2006, Zhang et al. 2010), but also can switch from the inactive to active state, enabling transcription of ncRNA, which plays a role in the proper functioning of the centromere (Han et al. 2009). Centromeric ncRNAs interact with many proteins i.a. CENP-A (Rošić et al. 2014), CENP-B (Carone et al. 2009), CENP-C (Du et al. 2010), HJURP (Quénet and Dalal 2014) and AURORA B (Ferri et al. 2009). For example, centromere inactivation in dicentric chromosomes or activation of neocentromeres in non-centromeric regions were reported (Williams et al. 1998, Nasuda et al. 2005, Marshall et al. 2008, Topp et al. 2009).

The results of studies on the epigenetic regulation of centromeric regions are ambiguous. The difficulty in studying these regions is caused by the fact that centromeres

Table 1. Epigenetic modifications of centromeric regions and their functions in plants and animals.

Epigenetic modification	Region	Function	Reference
histone variant CENH3 CENP-A	centromeric	specifies centromere location essential for kinetochore assembly	Gieni et al. 2008
H3K4me1, H3K4me2, H3K36me2, H3K36me3	centromeric	maintenance of centromere stability RNA II pol activity recruitment of HJURP proteins CENP-A deposition	Yan et al. 2005 Foltz et al. 2009
H4K5ac and H4K12ac	centromeric	CENP-A deposition	Shang et al. 2016
H4K20ac	centromeric	required for transcriptional activity required for kinetochore formation in human and *Gallus* cells	Shang et al. 2016
H2AT133ph H2AT120ph	centromeric	recruitment of Shugoshin (Sgo1) protein prevents precocious separation of sister chromatids	Kawashima et al. 2010
monoubiquitinated H2B (H2Bub1)	centromeric	required for transcriptional activity provides structural integrity required for proper chromosome segregation	Sadeghi et al. 2014
H3K9me	pericentromeric	chromatin condensation ensures chromatid cohesion provides structural integrity	Gieni et al. 2008
H4K20me	pericentromeric	chromatin condensation provides structural integrity	Gieni et al. 2008 Hori et al. 2014
H3K27me	pericentromeric	transcriptional repression of transposable elements	Jacob et al. 2010 Feng et al. 2017
H3 and H4 lysine residues acetylation	pericentromeric and centromeric	increase in chromatin compaction heterochromatin integrity	Gieni et al. 2008
Cytosine methylation of DNA	pericentromeric and centromeric	chromatin condensation provides structural integrity	Gieni et al. 2008 Song et al. 2013

in most multicellular eukaryotes are formed of numerous copies of repetitive sequences (Henikoff et al. 2001). Identification of individual epigenetic modifications is particularly difficult if the sequences of the same family of repeats have different epigenetic markers. For this reason, many studies do not present unequivocal results. There is also a limitation in the selection of methods to study these regions. For example, standard methods used to map DNA methylation, including high-throughput techniques based on microarrays and WGBS sequencing (bisulfite sequencing-based platforms), do not allow to assess methylation within highly repetitive DNA sequences. Therefore, in this case, immunofluorescence (IF) analysis is often used in combination with FISH (fluorescence *in situ* hybridization) on stretched DNA fibers (Koo et al. 2011).

Many studies on centromere chromatin in *Arabidopsis thaliana* (Linnaeus, 1753) have shown that it forms chromocentres in the interphase nuclei, it is rich in H3K9me2, characterized by DNA hypermethylation and enrichment in histone variant H2A.W (Probst et al. 2003, Stroud et al. 2013, Yelagandula et al. 2014). However, comprehensive IF studies using anti-5-methylcytosine antibody showed that the DNA in centromeric region is unmethylated. IF on the stretched fibers of the early pachytene chromosomes confirmed these observations, indicating that DNA sequences (178 bp tandem repeats) in the core regions with CENH3 were differently methylated than in the flanking pericentric regions. Regions in which CENH3 is present, and directly adjacent regions, are

unmethylated or significantly less methylated, while the remaining 178 bp repeats are highly methylated. Thus, DNA sequences in centromeric chromatin are hypomethylated compared to the sequences found in the flanking pericentric chromatin (Zhang et al. 2008). In addition, a correlation was found in Arabidopsis between the occurrence of 5mC and H3K9me2 in centromeric regions. Similar results were obtained while studying centromeric regions in maize. The methylation status of centromeric CentC repeats in maize is variable, whereby, similarly to Arabidopsis, DNA sequences associated with CENH3 in maize are hypomethylated (Koo et al. 2011).

In contrast, studies on centromeres in rice have shown that DNA sequences in a functional centromere can be both hypo- and hypermethylated. DNA methylation patterns appear to be correlated with specific sequence motifs (CG, CHG, CHH) in centromeric DNA (Yan et al. 2010). Detailed studies of the centromeric maize region have shown that there is a tendency of increased DNA methylation in CG and CHG motifs towards the centromere and decreased towards the chromosomal arms. This was also observed in *Populus trichocarpa* (Torrey et Grey, 1851) (Feng et al. 2010, Zemach et al. 2010). In turn, CHH methylation was relatively similar in different maize chromosomal domains, which was also confirmed by studies concerning rice centromere (Feng et al. 2010). Although general methylation level was similar in centromeres and pericentromeres, a slight increase in CG methylation and a decrease in CHG was observed in the centromeric core, with a marked difference between centromeres (Gent and Dawe 2012). This variation may result from the relative differences in the size of CentC sequence stretches in the individual centromeres (Jin et al. 2005).

Research on the level of DNA methylation in medaka fish (*Oryzias latipes* Temminck et Schlegel, 1846) demonstrated that centromeres are mainly hypermethylated, but have hypomethylated subregions (Ichikawa et al. 2017). It was found that DNA methylation patterns in centromeres were not correlated with the phylogenesis of centromeric sequences, but the hypo-/hypermethylated regions in individual chromosomes evolved independently by acquiring a unique sequence composition. In turn, examining methylation level in mouse cells, it was found that it depended on the type of tissue being tested. The highest level was observed in somatic cells, intermediate in sperm and the lowest in egg cells (Yamagata et al. 2007).

Centromeric chromatin (CEN) is characterized by the presence of specific histone H3 variant – cenH3 (CENP-A in mammals, CID (*centromere identifier*) in *Drosophila melanogaster* (Fallén, 1823), CENH3 in plants) (Steiner and Henikoff 2015). In multicellular eukaryotes, centromeres consist of alternating blocks of nucleosomes containing H3 or cenH3 (Blower et al. 2002, Sullivan and Karpen 2004, Alonso et al. 2007). The cenH3 nucleosomes recruit complexes that directly bind to cenH3, which in turn allows the attachment of numerous centromeric proteins termed CCAN (constitutive centromere-associated network) (Foltz et al. 2006, Carroll et al. 2009) (Fig. 1). The HJURP chaperone protein (Holliday junction recognition protein) is involved in the process of CENP-A deposition and complex formation between CENP-A and H4 (Shuaib et al. 2010). The structure of human CENP-A differs from canonical H3 histone, *inter alia*, by loop 1, which contains two additional amino acid residues (Arg80 and Gly81), affecting centromere chromatin stabilization (Tachiwana et al. 2011,

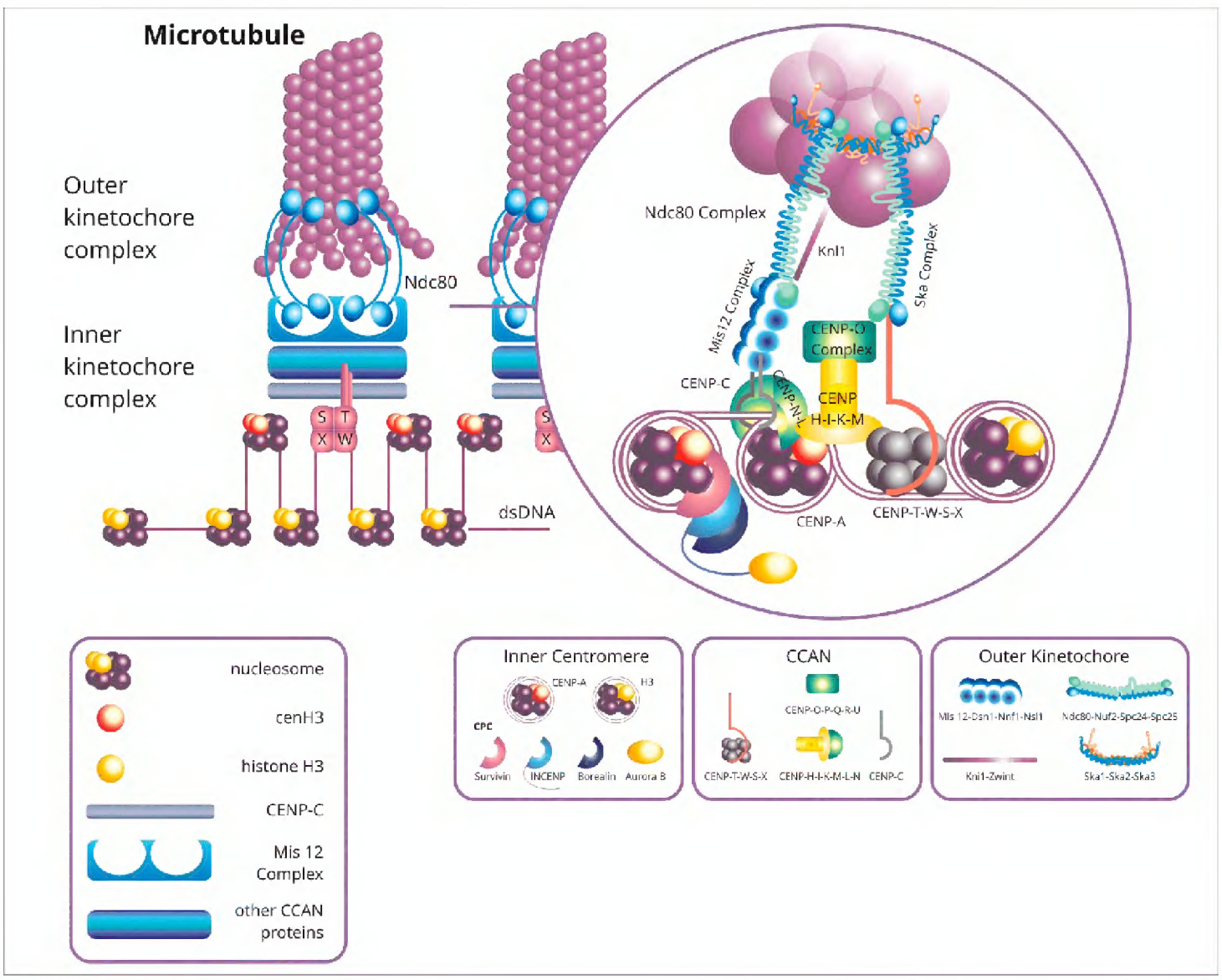

Figure 1. Model of the vertebrate mitotic centromere/kinetochore complex. Kinetochores assemble on chromatin marked by CENP-A containing nucleosomes. CENP-A nucleosome binds chromosomal passenger *complex (CPC), which consists of four proteins:* kinase Aurora B, INCENP, Survivin and Borealin. The kinetochore is composed mainly of CCAN (constitutive centromere-associated network) and Knl1-Mis12-Ndc80 complexes. The presence of CENP-A allows the recruitment of CCAN, which is a complex consisting of 16 centromeric proteins: CENP-C, CENP-T-W-S-X, CENP-H-I-K-M, CENP-N-L and CENP-O-P-Q-R-U. CENP-C and CENP-N bind CENP-A. The CENP-T-W-S-X complex creates a unique nucleosome-like structure that allows DNA binding in centromeric chromatin. CENP-N-L and CENP-H-I-K-M have regulatory roles. CENP-H-I-K-M-L-N help recruit CENP-C. CENP-C binds to the Mis12 complex, which then recruits Knl1 proteins interacting with microtubules and the Ndc80 complex. Ndc80 – kinetochore complex component (the complex consists of Ndc80-Nuf2-Spc24-Spc25 proteins); cenH3 – centromere specific histone 3 or histone H3 variant found at the centromere, CENP-A – centromere protein A, centromere specific histone 3 or histone H3 variant found at the centromere; CENP-C – centromere protein C; Mis 12 Complex – complex of the core kinetochore (the complex consists of *Mis12-Dsn1-Nnf1-Nsl1 proteins)*; Knl1 – *kinetochore* scaffold 1; Zwint – kinetochore proteins; CCAN – constitutive centromere-associated network, CPC – chromosomal passenger complex (consisting of Borealin, Survivin, INCENP, and the Aurora B kinase), INCENP – Inner Centromere Protein; Ska Complex – spindle and kinetochore associated (the complex consists of Ska1-Ska2-Ska3 proteins).

González-Barrios et al. 2012). CENP-A shows only 50% homology to H3 amino acid sequence. There is also variation in length and sequence of N- and C-termini among these proteins (Malik and Henikoff 2003), simultaneously the C-terminus retains the

hydrophobic region necessary for interaction with CENP-C (Kato et al. 2013). Moreover, it was shown that around the nucleosome containing CENP-A only 121 bp of the DNA is wrapped, 13 bp from both DNA ends are invisible in the crystal structure suggesting highly flexible ends (Tachiwana et al. 2011, Roulland et al. 2016). This structure disrupts the binding of histones H1 with the nucleosomes, allowing a more open configuration of the chromatin, which in turn enables the attachment of the CCAN complex (Roulland et al. 2016). Studies have shown that there are structural differences between CENP-A/H4 and H3/H4 heterotetramers (reviewed in Verdaasdonk and Bloom 2011). The presence of the CENP-A protein in the nucleosome ensures its more compact and rigid structure (Black et al. 2007). Similarly to CENP-A, plant centromeric CENH3 is characterized by significant variability between species (Malik and Henikoff 2009). CENH3 has a conserved histone-fold domain (HFD), instead the most significant differences in the structure of this protein in relation to H3 occur at the N-terminus (Ravi et al. 2010; Lermontova et al. 2014). This may be due to the fact that the C-terminus of CENH3 is responsible for histone H4 binding, which allows the formation of stable nucleosomes (Feng et al. 2019).

In human CEN chromatin, nucleosomes containing the CENP-A variant alternate with nucleosomes with the canonical histone H3. Histones H3 in this region undergo methylation at lysine positions 4 and 36 (H3K4me1, H3K4me2, H3K36me2, H3K36me3), characteristic of transcriptionally active chromatin. They affect RNA pol II (RNA polymerase II) activity and play an important role in the recruitment of HJURP proteins that participate in the CENP-A deposition (Bergmann et al. 2011, Duda et al. 2017). The absence of H3K4me2 in the centromere of artificial human chromosomes resulted in the inactivation of this centromere (Bergmann et al. 2011), which shows a functional link between epigenetic modification of CEN chromatin and maintaining centromere stability. Similarly, in plants, dimethylation of histone H3 at lysine 4 (H3K4me2) is a common modification in the centromeric H3 subdomains (Wu et al. 2011), which was not observed, for example, in the CENH3 subdomains of rice. It has even been hypothesized that the transcribed sequences located in the rice centromere can be a barrier preventing the introduction of CENH3 into the region of H3 subdomains. This separation of the CENH3 and H3 subdomains in the centromere core may be necessary for the formation of three-dimensional structure and functioning of rice centromere (Wu et al. 2011).

Interestingly, CEN is not usually associated with the presence of H3K9me2 or H3K4me3 heterochromatin markers, although H3K9me3 modification has been shown in this region to be associated with transcription repression (Bergmann et al. 2012). This illustrates that CEN chromatin can be both silenced heterochromatin as well as active euchromatin (Sullivan and Karpen 2004), however, it is important that the balance between them is preserved. Introduction of repressors or activators of transcription in artificial chromosomes disrupts the balance between modifications such as H3K4me2 and H3K9me3, which leads to the loss of the centromere function (Nakano et al. 2008).

In maize centromeres, the presence of histone post-translational modifications associated with transcriptional activity, such as histone H4 acetylation and H3K4me2, has been revealed. It was indicated that centromeres in this species are organized as eu-

chromatin regions flanked by pericentromeric H3K9me2-enriched heterochromatin (Yan et al. 2005). Histone H4 acetylation (H4K5ac and H4K12ac) was also detected in *Gallus* (Brisson, 1760) cells as a modification necessary for CENP-A deposition (Shang et al. 2016). It was shown that H4K20ac is essential for transcription of ncRNA, which is necessary for the deposition of CENP-A and kinetochores assembly in human and *Gallus* cells (Sullivan and Karpen 2004, Wang et al. 2008, Bergmann et al. 2011, Hori et al. 2014). Moreover, for the transcription of centromeric DNA monoubiquitination of lysine 119 in histone H2B (H2BK119ub1) must occur (Zhu et al. 2011, Sadeghi et al. 2014). It is mediated by the ubiquitin ligase E3 RNF20 (ring finger protein 20) in humans or Brl1 in *Schizosaccharomyces pombe* (Lindner, 1893) (Sadeghi et al. 2014). The H2BK119ub1 modification interacts with many proteins such as RNA pol II and SWI/SNF (switch/sucrose non-fermentable) protein complexes (Shema-Yaacoby et al. 2013), which contributes to the formation and maintenance of transcriptionally active chromatin. This modification also affects centromere integrity and accurate chromosome segregation. It has been shown that the decrease in RNF20 level results in H2BK119ub1 deficiency in this region, which in turn causes heterochromatin formation, thereby reducing the transcription of the centromeric DNA sequence and resulting in an abnormal chromosome segregation in human and *S. pombe* (Lindner, 1893) cells (Sadeghi et al. 2014, Zhang et al. 2017).

CENP-A is less likely to undergo post-translational modification than canonical histone H3 (Fig. 2). This is due to, *inter alia*, the lower lysine content in CENP-A. In histone H3, up to 17 different types of post-translational modifications were found (Xu et al. 2014), whereas only four modifications were detected in CENP-A: methylation, acetylation, phosphorylation and ubiquitination (Srivastava and Foltz 2018). The most characteristic CENP-A modifications are Gly1 trimethylation, Ser 7, 16, 18 and 68 phosphorylation and monomethylation, acetylation and *ubiquitination* of lysine 124. These CENP-A-specific modifications, play an important role in chromosome segregation during cell division, because they regulate CENP-A deposition in centromeric chromatin and participate in CCAN recruitment (Srivastava and Foltz 2018).

It has long been believed that centromeric chromatin is transcriptionally inactive because it is formed mainly by satellite sequences. It is now known that CEN transcription is mediated by RNA pol II, which was detected in centromeric regions in both *S. pombe*, *Drosophila*, mouse, human, *Zea* (Linnaeus, 1753), *Oryza* (Linnaeus, 1753) and neocentromeres, as well as in CEN of human artificial chromosomes (HAC) (Chueh et al. 2009, Ferri et al. 2009, Ohkuni and Kitagawa 2011, Chan and Wong 2012, Podgornaya et al. 2013, Quénet and Dalal 2014, Rošić et al. 2014). The important role of transcription in centromere integrity was shown by numerous studies on its inhibition, which resulted in the loss of centromere function (Quénet and Dalal 2014, Rošić et al. 2014, Sadeghi et al. 2014). Many genes have been identified in the centromeric regions of various plants, including rice (Jiang 2013) and *A. thaliana* (May et al. 2005). Transcribed centromeric elements can activate the process of RNAi by forming siRNA (small interfering RNA) and affecting both DNA and histone modifications in the centromeric region (Lippman and Martienssen 2004).

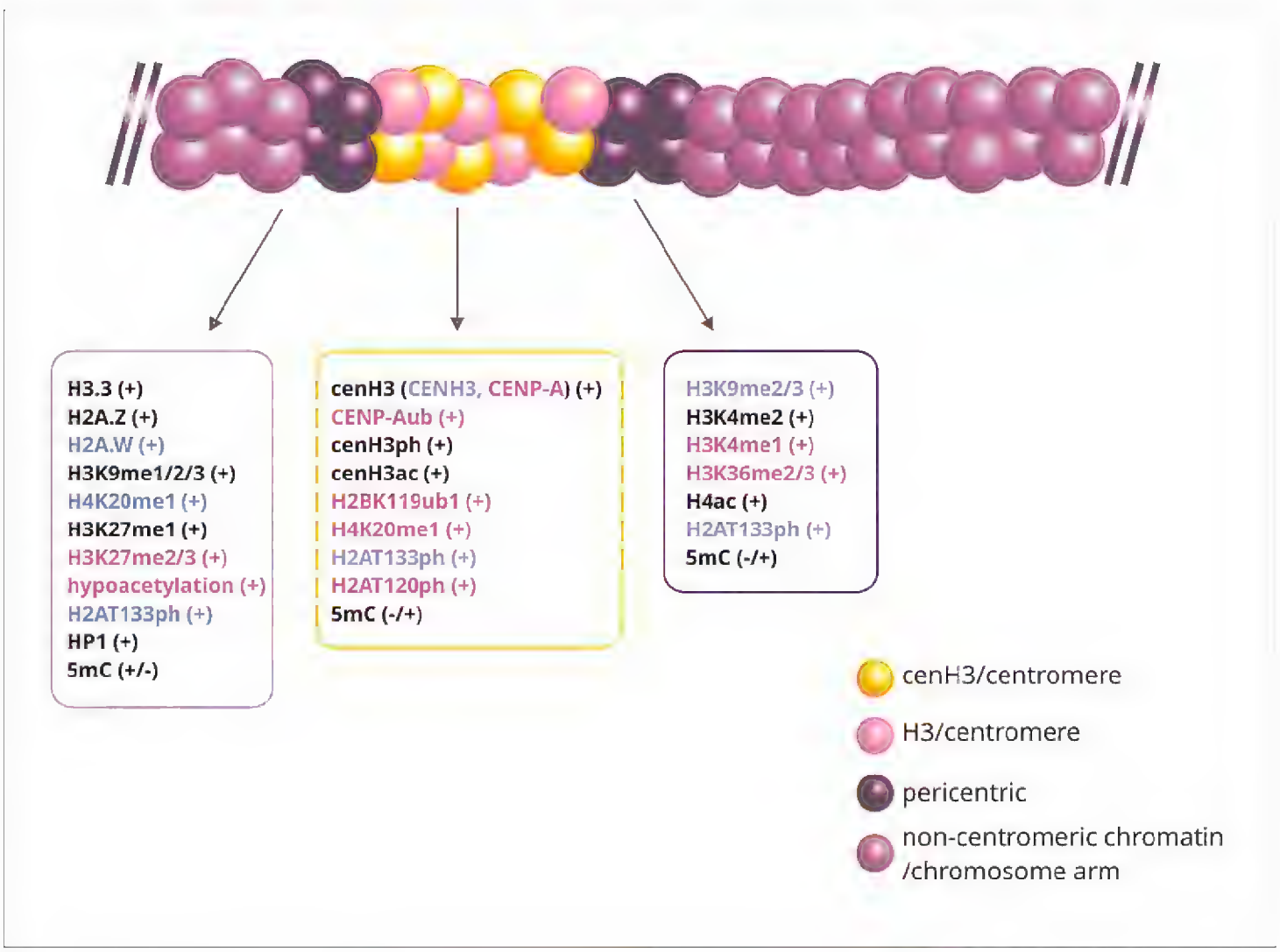

Figure 2. Epigenetic modifications in centromeric and pericentric chromatin. Centromeres consist of alternating blocks of nucleosomes containing H3 or cenH3. At pericentric sites, only H3-containing nucleosomes are present. Epigenetic markers in centomere and pericentromere regions characteristic for both plants and animals are marked with black color, only for plants with violet color, only for animals with rose color. (+) epigenetic marker always present; (-/+) epigenetic modification present or absent.

Studies also showed transcriptional activity of centromeric retrotransposons that affect the formation, stabilization and functioning of centromeres (Jiang et al. 2003, Topp et al. 2004). An example is the CRM transcript in maize, which contributes to the stabilization of centromere chromatin (Topp et al. 2004) or the CRR transcript in rice that is involved in the formation and maintenance of centromeres through RNAi pathway (Neumann et al. 2007). The additional evidence, that transcription of centromeric DNA is common, is the presence of H3K4me2 modification in this region of many plants (onion, rice, Arabidopsis, maize). Maintaining CEN chromatin in the active state and its transcription is also necessary for the replacement of histone H3 with cenH3 (Quénet and Dalal 2014, Bobkov et al. 2018). The lack of centromeric transcripts leads to disturbances during mitosis (Quénet and Dalal 2014). Centromeric chromatin is transcriptionally active even during mitotic division (Chan et al. 2012), which ensures stability of kinetochores and coherence of centromeres (Liu et al. 2015). Phosphorylation of centromeric histone H2A (H2AT120ph in animals, H2AT133ph in plants) by the Bub1 (budding uninhibited by benzimidazoles 1) kinase is required for the recruitment of the Shugoshin protein (Sgo1). This protein ensures chromatid

coherence in internal centromeres (Kawashima et al. 2010). Sgo1 interacts with RNA pol II and is directed to the inner centromere between two sister chromatids. The open chromatin structure in the centromeric region allows binding of the Sgo1 protein to cohesin and provides protection against premature chromatid separation (Kang et al. 2011, Liu et al. 2015). Initiation of centromeric DNA transcription must be preceded by chromatin remodeling. An important factor in this process is a histone chaperone, FACT (facilitates chromatin transcription) (reviewed in Reinberg and Sims 2006). FACT allows transcription through the destabilization of nucleosomes, allowing polymerase to access DNA (Belotserkovskaya et al. 2003). After polymerase passes, it allows a return to the earlier chromatin structure (Jamai et al. 2009).

It has also been proven that the region directly adjacent to the centromere plays a role in sister chromatid cohesion (Bernard et al. 2001, Steiner and Henikoff 2015). Between the prophase and anaphase, sister chromatids are kept together in pericentromeres after cohesins are removed from other chromosome regions (Nasmyth and Haering 2009). There are known various epigenetic mechanisms associated with chromatin silencing that provide cohesion maintenance in pericentromeres (HP1-*heterochromatin protein 1*, H3K9me3, RNAi) (Mosch et al. 2011). Changes in this region may lead to impairment of proper chromosome segregation (Allshire et al. 1995, Steiner and Henikoff 2015). However, there are hypotheses that this heterochromatin region is necessary to establish the centromere, but is not required to retain it (Folco et al. 2008). In addition, studies on neocentromeres, which can form in euchromatin areas, indicate that pericentromeric heterochromatin (PHC) is not necessary for the proper functioning of the centromere (Shang et al. 2013). Nevertheless, it is believed, that pericentromeric heterochromatin regions may play a role in preventing the centromere from spreading to adjacent regions (Sullivan 2002). From an epigenetic point of view, pericentromeres show a greater similarity to centromeres than to other chromosomal regions. This is reflected in siRNA transcription, DNA methylation and some post-translational modifications of histones. Although there is evidence that centromeres may function independently of pericentromeres, as found, for example, in studies conducted on *S. cerevisiae* (Weber et al. 2004), there is a strong interdependence of these two regions (Han et al. 2006).

Histones in pericentric chromatin are mostly hypoacetylated, which causes chromatin condensation. Pericentromeric areas are characterized by the presence of histone variants H3.3 and H2A.Z (Drané et al. 2010, Santenard et al. 2010), modifications of histones such as mono-, di- and trimethylation of H3K9, H3K27 and H4K20 (Feng et al. 2017) and a high level of 5-mC in DNA (Song et al. 2013). These modifications are characteristic of transcriptionally inactive chromatin and play a role in the silencing of genetic mobile elements occurring abundantly in these chromosomal regions (Roudier et al. 2011, Rose and Klose 2014, Feng et al. 2017). For example, monomethylation of lysine 27 in histone H3 is associated with constitutive repression of transcription. This was confirmed by the study of pericentromeric regions of polytene chromosomes of *Drosophila*. They correspond to green – inactive (the division of chromatin into the following shades: red, yellow, blue, green and black; according to Filon et al. 2010) or ruby chromatin (the division of chromatin into the following shades: aquamarin,

lazurite, malachit and ruby; according to Zhimulev et al. 2014), which is characterized by H3K27 methylation as well as SU(VAR)3-9 and HP1 presence (Boldyreva et al. 2017). Loss of H3K27 methylation in the pericentromeric regions causes transposons reactivation (Jacob et al. 2010). This may result in a cancer or other diseases such as ICF (immunodeficiency, centromere instability, facial anomalies). ICF is a rare autosomal recessive disease characterized by a lack of DNMT3B activity. DNA methylation depletion results in the loss of repressive histone modifications (often H3K27me3) and the appearance of modifications characteristic of euchromatin (H3K9ac, H3K4me), which further leads to reactivation of transposons (Jin et al. 2008).

A characteristic protein of this region is HP1 or its homologs (Guenatri et al. 2004, Cam et al. 2005), which affect the stabilization and maintenance of the heterochromatic state (Saksouk et al. 2015) of pericentromeric regions. The HP1 protein interacts with the Suv39h histone methylation kinase, which catalyzes the trimethylation of lysine 9 in H3 (Aagaard et al. 1999, Grewal and Jia 2007). In mice, it has been found that Suv39h deficiency results in a lack of H3K9me3, disrupting the occurrence of HP1 in the pericentromeric heterochromatin, which in turn translates into abnormal chromosomal segregation (Peters et al. 2001, Maison et al. 2002). The heterochromatic nature of the pericentromeric region is also confirmed by the analysis of marker gene expression. Inserted into the pericentromeric region, they are transcriptionally silenced, while the insertion of the same genes into the CEN region shows a significantly weaker silencing effect (Allshire et al. 1995).

The analysis of human neocentromeres that showed centromere functioning without satellite repeats (although they had a slightly higher AT content, from 59.9 to 66.1% compared to genomic average of 59%). The acquisition of centromeric function by a chromatin region without changing the DNA sequence was called the "centromerization" phenomenon (Choo 2000). Such neocentromeres, formed outside the centromeric regions, while maintaining the characteristics of the original centromere without the underlying centromere DNA, were also observed in animals and plants (*Gallus* (Brisson, 1760), *Equus* (Linnaeus, 1758), *Solanum* (Linnaeus, 1753), *Hordeum* (Linnaeus, 1753), *Avena* (Linnaeus, 1753) and *Zea* (Linnaeus, 1753)) (Nasuda et al. 2005, Ishii et al. 2008, Kagansky et al. 2009, Topp et al. 2009, Piras et al. 2010, Gong et al. 2012, Fu et al. 2013, Shang et al. 2013). The existence of neocentromeres and rapid evolution of centromeric DNA suggest that these are epigenetic mechanisms, rather than DNA sequence itself, that determine centromere functions (Piras et al. 2010).

Studies on dicentric chromosomes also support this fact. Dicentric chromosomes are the result of genomic rearrangements placing two active centromeres on the same chromosome. Most dicentric chromosomes are unstable and only due to epigenetic mechanisms, which deactivate one of the centromeres, monocentric chromosomes can be formed that normally segregate during cell division (Sullivan and Schwartz 1995, Chiatante et al. 2017). If one of the centromeres is not turned off, the chromosome breaks during division. DNA sequences of the active and inactive centromeres of dicentric chromosomes are almost identical, but the centromere activity states are completely different. Centromere inactivation on the dicentric chromosome is carried out

by H3K27me2 and H3K27me3. Smaller centromeres appear to be inactivated more frequently than the larger ones (Han et al. 2009). It was confirmed by analyses of dicentric chromosomes in plants e.g. *Zea mays* (Linnaeus, 1753), (Han et al. 2006), *Oryza sativa* (Linnaeus, 1753) (Wang et al. 2013) and in humans. This explains some processes regarding the formation and maintenance of neocentromeres in human, because neocentromeres are always smaller than the native ones. If small centromeres are more susceptible to inactivation compared to larger ones, then most of the newly formed neocentromeres will be inactivated during subsequent cell divisions (Zhang et al. 2010).

Evolutionary repositioning or shift of the centromere along the chromosome with its function, leading to the formation of new evolutionary centromeres (ENCs), is another phenomenon that shows the epigenetic nature of these structures. This phenomenon was observed in primate chromosomes, other placental, marsupials and birds (Montefalcone et al. 1999, Ventura et al. 2007, Piras et al. 2010, Zlotina et al. 2012). The beginning of repositioning causes the loss of the function of the original centromere, followed by epigenetic changes in the non-centromeric position, leading to the formation of a new functional centromere in the chromosome region devoid of satellite DNA (Montefalcone et al. 1999). The resulting neocentromere may gradually accumulate repetitive DNA sequences through recombination mechanisms during evolution (Piras et al. 2010). Accumulation of these sequences probably ensures the stabilization of the centromere during cell division (Marshall et al. 2008), facilitates incorporation of histone cenH3 (Steiner and Henikoff 2015) and the accuracy of chromosomal segregation (Piras et al. 2010). All these reports shed more light on the role of satellite sequences. Despite their heterogeneity between species, a common pattern of structural DNA motifs required for centromere specification begins to be noticed (Black and Giunta 2018, Oliveira and Torres 2018). This hypothesis is supported by the fact that *de novo* chromosome formation revealed preferential centromere occurrence in areas built of tandem repeats (Grimes et al. 2002, Masumoto et al. 2004, Nagaki et al. 2004, Han et al. 2009).

Telomere and subtelomere

Telomeres are specialized structures located at the ends of linear eukaryotic chromosomes. Their function is to protect the ends of chromosomes from inappropriate enzymatic degradation. They are also responsible for chromosome localization in the cell nucleus and transcription regulation of genes located near telomeres (Deng et al. 2008, Fojtová and Fajkus 2014). Telomeres also protect chromosomes from fusions, formation of dicentric chromosomes and homologous recombination (Artandi and DePinho 2010). While telomere function has been well known for a long time, the role of the subtelomeric region is still being investigated. It is indicated that subtelomeres support telomeres in their function, because they may affect processes such as cell cycle regulation, cell aging, motility and chromosomal localization in the nucleus (Riethman et al. 2005).

Due to the important functions they perform in the cell, telomeres are evolutionarily conserved regions and their structure is only slightly different in individual species.

However, the length of telomeric sequences shows individual, tissue and cellular variability (Marión and Blasco 2010). Telomeres contain a double-stranded region composed of tandem DNA repeats, which can be described by the following formula: 5'-T_x(A)G_y-3' (x, y – number of repeats) and single-stranded free 3' end rich in guanine (G-overhang) (Wang and Zakian 1990, Smogorzewska and de Lange 2004), whose length varies from 16 to 200 nt depending on the species (Kazda et al. 2012). There are, however, exceptions from the above formula for telomere monomers, e.g. in *Allium cepa* (Linnaeus, 1758) this is the $(CTCGGTTATGGG)_n$ sequence (Fajkus et al. 2016), in *Genlisea* (Bentham and Hooker, 1883) two sequence variants TTCAGG and TTTCAGG (Tran et al. 2015) and in *Ascaris lumbricoides* (Linnaeus, 1758) – TTAGGC (Müller et al. 1991). In general, however, it is assumed that this sequence in vertebrates consists of $(TTAGGG)_n$ tandem repeats (Moyzis et al. 1988), $(TTAGG)_n$ in arthropods (Kuznetsova et al. 2015), and in most plants – $(TTTAGGG)_n$ (Richards and Ausubel 1988). The telomere sequence is usually very homogeneous, particularly in contrast to the subtelomeric sequences constituting a border region between the telomere and the region where genes are located. The subtelomeric regions include a fragment of about 500 kb (Macina et al. 1994) and similarly as telomeres, it consists of repetitive DNA sequences. However, the presence of genes and CpG islands has not been found in telomeres, while the subtelomers are characterized by the presence of a small number of genes and CpG islands (Blasco 2007). The common feature of the subtelomeric regions of various eukaryotic organisms is the presence of long arrays of tandem repetitive (TR) sequences or duplicated DNA fragments, which also include telomeric sequence motifs (Torres et al. 2011).

In mammals, the DNA stretch comprising a telomere is terminated with single-stranded free G-overhangs of varying, species-specific length (Kazda et al. 2012). G-overhangs are important for telomere maintenance, acting as a primer for telomerase (Lingner and Cech 1996). These 3' ends form a spatial structure called the G-quadruplex (G4-DNA), which protects the telomere from exonucleases, thereby protecting the DNA strand against degradation (Sen and Gilbert 1988), and also inhibits telomerase activity (Zahler et al. 1991).

Telomeric chromatin has a typical organization, forming the nucleosome fiber at the basal level. This structure may be different only in regions where there are telomere-specific proteins (Pisano et al. 2007). Telomere structure is formed with the participation of a protein complex called shelterin (Fig. 3). The complex consists of six proteins: TRF1 and TRF2 (telomere repeat-binding factor 1 and 2) (Zhong et al. 1992, Chong et al. 1995, Bilaud et al. 1997), RAP1 (repressor/activator protein 1), TIN2 (TRF1-interacting nuclear factor 2) (Kim et al. 1999, Li et al. 2000), TPP1 (TINT1/PTOP/PIP1 protein) (Houghtaling et al. 2004) and POT1 (protection of telomeres 1) (Baumann and Cech 2001). TRF1 and TRF2 proteins bind to telomere double-stranded DNA, while other proteins stabilize the structure of the shelterin complex. The interaction between telomere DNA and shelterin proteins first of all protects and stabilizes telomere structure, and secondly, regulates the access of proteins involved in DNA repair and elongation (de Lange 2005). Double-stranded telomeric sequence, due to interactions with shelterin proteins, folds and closes forming a larger T-loop.

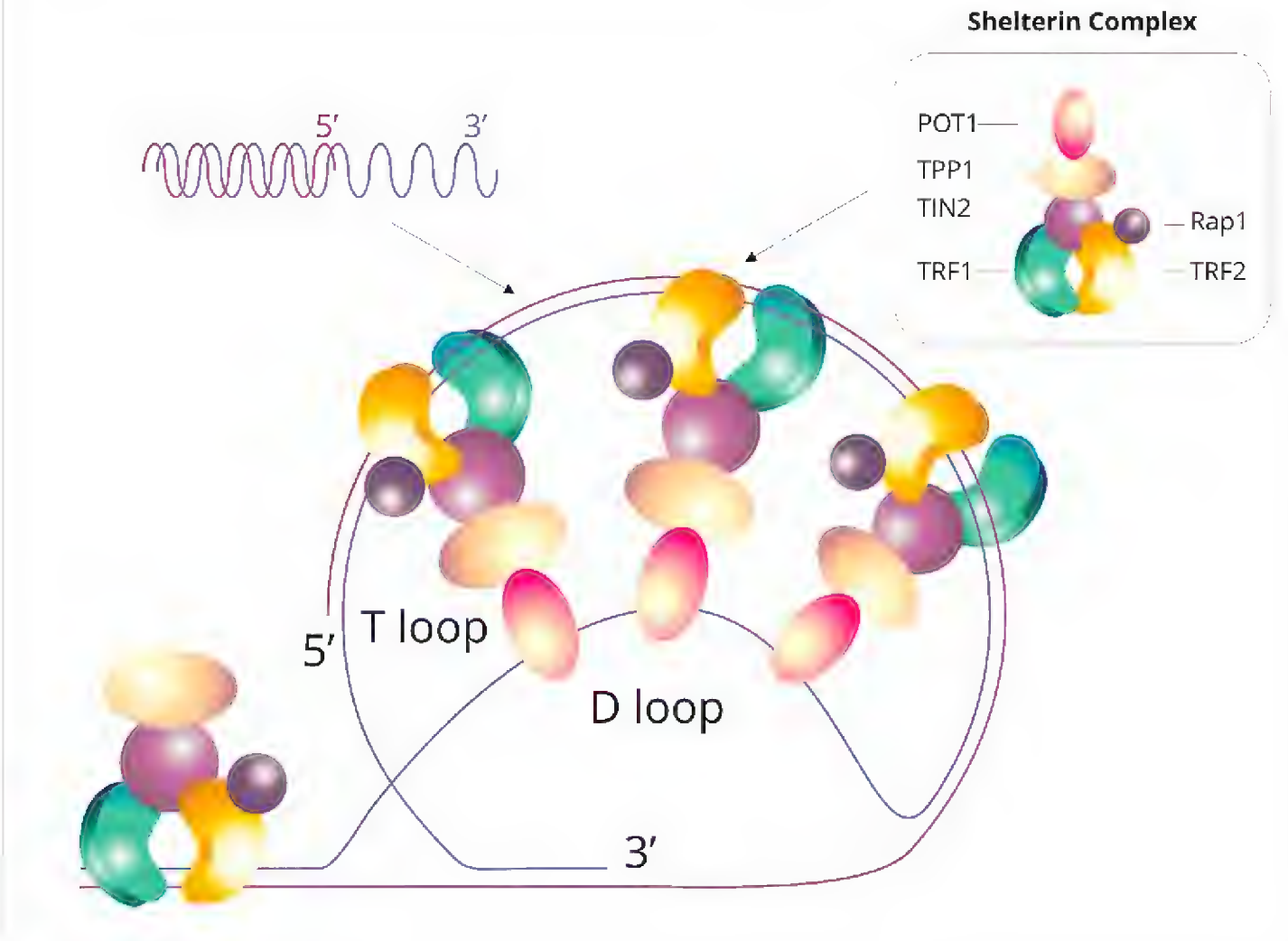

Figure 3. Telomere structure in mammals; T-loop and D-loop are presented together with schematic representation of the shelterin complex on telomeric DNA. The shelterin complex consists of six proteins: TRF1 and TRF2 (telomere repeat-binding factor 1 and 2), RAP1 (repressor/activator protein 1), TIN2 (TRF1-interacting nuclear factor 2), TPP1 (TINT1/PTOP/PIP1 protein) and POT1 (protection of telomeres 1).

In turn, the free 3' overhang at the end of the chromosome in the T-loop binds to the double-stranded telomere fragment to form a smaller D-loop. It has been found that the T-loops are characteristic of eukaryotic organism telomeres, although it is not certain whether they are present in all of them (de Lange 2004).

D. melanogaster telomeres have yet another structure. Three following retrotransposons have been identified in the telomere sequence: HeT-A, TART and TAHRE (HTT). At the ends of telomeres, there are numerous copies of HTT retrotransposon, while in the most proximal region, there are sequences called TAS (telomere associated sequence). The ends of telomeres are protected and stabilized by a protein complex. An important role is played by the heterochromatin 1 (HP1) protein, which binds to dimethyl lysine 9 in histone H3 (H3K9me2) (Vermaak and Malik 2009). Its absence contributes to the fusion of *Drosophila* chromosomes (Fanti et al. 1998).

In plants, telomeres are usually several kbs in size (*A. thaliana* – 2–9 kb), although they may be longer in some plants, e.g. tobacco telomeres may have a size of up to 150 kb (Richards and Ausubel 1988, Fajkus et al. 1995). G-overhang size may be 20–30 nt, however, it may not be present in all telomeres (Riha et al. 2000). Studies have shown that several proteins bind to telomeric dsDNA (double stranded DNA) as well as G-rich ssDNA (*single stranded DNA*), but they are not fully characterized.

Two proteins are known that bind to single-stranded telomeric sequences: GTBP1 (G-strand specific single stranded telomere-binding protein 1) and STEP1 (single stranded telomere-binding Protein 1) (Kwon and Chung 2004, Lee and Kim 2011). Homologs of the POT1 protein, which forms a heterodimer with the TPP1 protein have been also detected (Wang et al. 2007). Studies of the function of these proteins in *A. thaliana* showed that the POT1a homologue binds telomerase and is involved in the synthesis of telomere repeats, while the POT1b and POT1c homologs are involved in the protection of chromosome termini (Shakirov et al. 2005, Kobayashi et al. 2019). In *A. thaliana*, TRB proteins (telomere repeat-binding factors) were also identified (Mozgová et al. 2008), containing a conserved domain similar to the telobox-type Myb (short telomeric motif, Myb-related DNA-binding domain) (Peška et al. 2011), through which they bind to telomeric dsDNA. This domain is typical for mammalian TRF1 and TRF2 proteins, although differently located. In TRB proteins, it is present at the N-terminus and in TRF, at the C-terminus. In addition, TRB proteins were found to possess a histone-like domain (H1/5) that plays a role in DNA-protein reactions and interaction with POT1b (Schrumpfova et al. 2008).

Epigenetic regulation of telomere and subtelomere regions

The epigenetic nature of telomeres and subtelomeres remains controversial (Vaquero-Sedas and Vega-Palas 2011, Galati et al. 2013, Ichikawa et al. 2015, Adamusová et al. 2019). In the classic model, animal and plant telomeres were interpreted as heterochromatic structures (Kavi et al. 2005, Postepska-Igielska et al. 2013). However, more and more data indicate their dual character, showing modifications of histones characteristic of both the eu- and heterochromatin fraction (Vrbsky et al. 2010) (Fig. 4). Some studies even indicate that telomeres may exhibit mainly euchromatin traits, while subtelomeres – heterochromatin features (Vaquero-Sedas et al. 2011). However, this is not definitively established, especially that even the level and occurrence of DNA methylation within telomeres remains unexplained (Blasco 2007, Vrbsky et al. 2010, Vaquero-Sedas et al. 2012, Ogrocká et al. 2014).

The variety of information regarding telomere regions may partly result from experimental limitations, but also due to the epigenetic diversity of animal (Cubiles et al. 2018) and plant cells (Majerová et al. 2014). Difficulty in determining the epigenetic state of telomeric chromatin also results from the presence of interstitial telomere repeats (ITRs) within the internal regions of chromosomes. Most of the ITRs were found within or adjacent to the constitutive heterochromatin (Meyne et al. 1990, Rodionov et al. 2002, Galkina et al. 2005, Vaquero-Sedas and Vega-Palas 2011). ITR sequences differ from typical telomere sequences in that they are heterogeneous, degenerate and contain other sequence types in addition to telomere sequence repeats (Lin and Yan 2008, Vega-Vaquero et al. 2016).

Telomeric and subtelomeric chromatin studies in mouse showed the presence of histone modifications characteristic of the heterochromatin fraction (Garcia-Cao et al. 2004, Gonzalo et al. 2006). Telomeres in vertebrates, as well as in *D. melanogaster*,

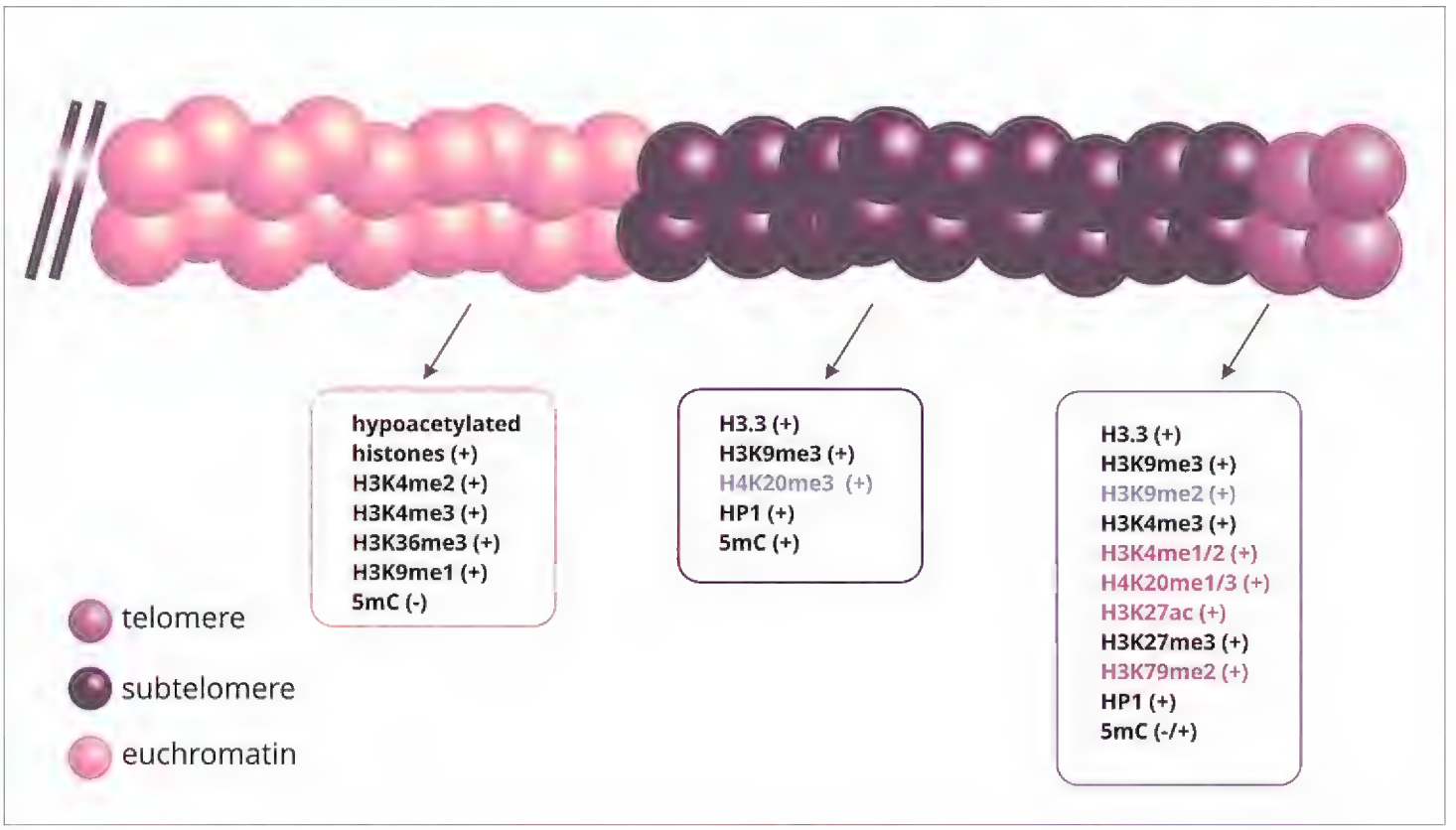

Figure 4. Epigenetic modifications in telomere and subtelomere chromatin and adjacent euchromatin. Epigenetic markers in telomere and subtelomere regions characteristic for both plants and animals are marked with black color, only for plants with violet colour, only for animals with rose color.

are rich in H3K9me3 (Peters et al. 2001, Garcia-Cao et al. 2004). This modification is recognized by heterochromatic protein 1 (HP1), which can recruit histone methyltransferases (HMTase) such as SuM4-20h1 and SuM4-20h2, which methylate H4 at lysine 20 (H4K20me3) (Nakayama et al. 2001, Benetti et al. 2007). In telomeres, Dot1L HMTase mediates methylation of lysine 79 in H3 (H3K79me2) (Shanower et al. 2005) and methylates lysine 20 in H4 (H4K20me3) (Jones et al. 2008). In addition, histones H3 and H4 are not strongly acetylated in telomeres (Benetti et al. 2007). In human telomeres that lack SIRT6 deacetylase, a higher level of H3K9 acetylation is observed, which usually leads to telomere dysfunction (Michishita et al. 2008).

However, in mouse cells, telomeres are enriched in modifications specific to heterochromatin (H3K9me3) and euchromatin (H3K4me3). Although the H3K4me3 modification was at a lower level compared to H3K9me3 (Cao et al. 2009). ChIP-seq analysis of telomeres of various human cells has shown that they are characterized by low levels of H3K9me3, typical of heterochromatic regions, while they are enriched with euchromatin H4K20me1 and H3K27ac modifications (Rosenfeld et al. 2009, O'Sullivan et al. 2010, Cubiles et al. 2018).

Similar results were obtained in studies on plant telomeres. In Arabidopsis, heterochromatin modifications, such as H3K9me2 and H3K27me3, as well as euchromatin H3K4me3 modification have been reported (Vrbsky et al. 2010, Majerová et al. 2014, Adamusová et al. 2019). This occurrence of both heterochromatin and euchromatin modifications in the Arabidopsis telomere region was defined as the presence of an "intermediate" heterochromatin (Vrbsky et al. 2010, Majerová et al. 2014). Subsequent studies have shown that histones in telomeres have modifications typical of euchro-

matin, while histones within ITR regions possess modifications typical of condensed chromatin (Vaquero-Sedas et al. 2012). In the case of *Ballantinia antipoda* (Mueller, 1974), the H3K9me2 heterochromatin modification occurred mainly in telomeres, and H3K4me3 was found at a lower level, whereas only the H3K9me2 modification was present in the ITR region. Thus, it can be concluded that the chromatin of telomeres has both euchromatin and heterochromatin epigenetic markers, while the ITR regions are mainly heterochromatic (Majerová et al. 2014). In *A. thaliana* (Vrbsky et al. 2010) and *Nicotiana tabacum* (Linnaeus, 1753) telomeres, in addition to H3K9me2 and H3K4me3 modifications, the presence of H3K27me3 modifications was found, typical for heterochromatin, and it also occurs in human telomeres (Boros et al. 2014), although it is absent in mouse telomeres (Saksouk et al. 2014). Recent studies of human telomeres revealed that the PRC 2 (Polycomb 2) complex is responsible for the occurrence of H3K27me3, which affects the H3K9me3 heterochromatic modification to recruit HP1 to heterochromatin (Boros et al. 2014). It was also found that the TERRA transcript (TElomeric Repeat-containing RNA) is necessary for telomeric heterochromatin formation, the amount of modifications such as H3K9me3, H4K20me3 and H3K27me3 depends on the level of the TERRA transcript (Montero et al. 2018). It was found that lower levels of this transcript were associated with a decrease in the level of heterochromatin modifications in telomeres, H3K9m3 in particular (Deng et al. 2009).

Studies on telomere DNA methylation have not found so many discrepancies. Telomeres in mammalian cells are deprived of CpG dinucleotides, and therefore do not undergo DNA methylation (Draskovic and Londono-Vallejo 2013). Methylation studies of telomere sequences in plants have yielded conflicting results. Cytosine methylation in telomere CCCTAAA repeats was found in *A. thaliana* (Cokus et al. 2008), *N. tabacum* (Majerová et al. 2011), as well as in some other plants (Majerová et al. 2014). In turn, other studies on *A. thaliana* telomere DNA revealed low or no methylation (Vega-Vaquero et al. 2016). Detailed studies have shown that ITR sequences and sequences at the border of the telomere/subtelomere region are characterized by high levels of cytosine methylation (Cokus et al. 2008, Vrbsky et al. 2010, Vaquero-Sedas et al. 2012, Ogrocká et al. 2014). Very low level of genomic DNA methylation caused disturbances in telomere homeostasis in *A. thaliana* (Ogrocká et al. 2014, Xie and Shippen 2018), while no such changes were observed in *N. tabacum* (Majerová et al. 2011). This shows the differences in the role of DNA methylation in the regulation of telomere homeostasis in various plants (Fojtová and Fajkus 2014, Procházková-Schrumpfová et al. 2019).

While there is great controversy about the heterochromatic nature of telomeres, most studies show that this chromatin fraction is characteristic of subtelomeric regions. In animal and human cells, the subtelomeric regions are characterized by high CpG methylation and trimethylation of lysine 9 in histone H3 (H3K9me3) (Gonzalo et al. 2006). They can have a silencing effect on the expression of adjacent genes, as well as TERRA transcription. This silencing is defined as the telomere position effect (Azzalin et al. 2007, Cubiles et al. 2018). The analysis of most plant subtelomeric regions has also shown a high level of DNA methylation (Majerová et al. 2014, Ogrocká et al. 2014).

The heterochromatic state plays an important role in telomere biology, suggesting that the integrity of the subtelomeric heterochromatin may be important for the proper func-

tioning of telomeres. A correlation was found between changes in the level of DNA methylation in the subtelomeric region and regulation of telomere length (Garcia-Cao et al. 2004, Gonzalo et al. 2006). In Arabidopsis, the subtelomeric region regulates the telomere length homeostasis. Genome hypomethylation in *A. thaliana* caused shortening of telomeres, although it was not so extensive to lead to genomic or chromosomal instability (Fajkus et al. 1995, Ogrocká et al. 2014). It has also been shown that post-translational modifications of histones have no effect on telomere length in *N. tabacum* (Majerová et al. 2011).

In budding yeasts, heterochromatinization of the subtelomeric region positively regulates telomere length (Nislow et al. 1997). For animals the opposite is true, a decrease in the occurrence of heterochromatin markers, including DNA methylation in the subtelomeric region, correlates with telomere elongation and increased recombination (Gonzalo et al. 2006, Benetti et al. 2007, Blasco 2007, Ng et al. 2009). An example is the research by Gonzalo et al. (2006), showing elongated telomeres with reduced methylation of the subtelomeric regions. Mouse mutants lacking DNA methyltransferases DNMT1 or DNMT3A and DNMT3B have very long telomeres and exhibit ALT (alternative lengthening of telomeres) characteristics, i.e. an increased rate of T-SCE (telomeric sister chromatin exchange) and the presence of APB (ALT-associated PML body) (Gonzalo et al. 2006).

Surprisingly, different reports have indicated that the length of telomeres does not change in epigenetic mutants (Roberts et al. 2011), or shown the association of very short telomeres with hypomethylation of subtelomeric regions (Benetti et al. 2007) or global hypomethylation (Pucci et al. 2013). In addition, telomere elongation has been linked to DNMT3A targeting to subtelomeric regions, resulting in increased DNA methylation (Cubiles et al. 2018).

For a long time, telomeres were perceived as silenced, transcriptionally inactive chromosome segments. This fact is negated by the presence of telomeric RNAs containing UUAGGG repeats, called TERRA, which are transcribed from the subtelomeric regions towards the ends of the chromosome by RNA pol II in yeasts, vertebrates and plants (Azzalin et al. 2007, Luke et al. 2008). The prevalence of these transcripts suggests that this is a conservative trait associated with an important function in telomere biology (Azzalin et al. 2007, Luke et al. 2008). Two classes of TERRA promoters were found in the chromosomes, and their expression is regulated by CTCF (CCCTC-binding factor) and RAD21 cohesin (radiation-sensitive 21) (Deng et al. 2012, Porro et al. 2014, Bettin et al. 2019). Absence or decrease in RAD21 or CTCF levels results in the loss of RNA pol II binding to TERRA promoters, resulting in the reduction in TERRA expressi regions, therefore, an increase in DNA methylation in this region is associated with a decrease in the expression level (Yehezkel et al. 2008, Nergadze et al. 2009, Farnung et al. 2012). The correlation was shown between inhibition of TERRA transcription and the presence of H3K9me3, H4K20me3 and DNA methylation in telomeric and subtelomeric regions (Schoeftner and Blasco 2008, Nergadze et al. 2009, Farnung et al. 2012). Moreover, it turned out that histone acetylation and DNA hypomethylation positively affect the TERRA transcription process (Azzalin and Lingner 2008). Hypomethylation of subtelomeric sequences in mammalian cells lacking DNA

methyltransferases leads to TERRA overexpression. In mouse, TERRA transcript level in cell lines with deficiency of Suv3-9h and Suv4-20h HMTase is elevated compared to wild-type mouse cells. The level of epigenetic modifications characteristic for heterochromatin also regulates TERRA transcription in yeasts (Cusanelli and Chartrand 2014). In yeast, TERRA transcripts are maintained at a low level by Rat1 (Luke et al. 2008), the Sir2/Sir3/Sir4 sirtuin complex (histone deacetylases) and Rif1 and Rif2 (Rap1-interacting factor 1 and factor 2) (Iglesias et al. 2011). These results suggest that TERRA expression depends on the epigenetic status of subtelomeres and telomeres (Iglesias et al. 2011, Arnoult et al. 2012).

Binding of the TERRA transcripts to telomeres seems to be crucial for their structure and function (Luke et al. 2008). TERRA transcripts can negatively impact telomeres elongation. TERRA is believed to bind to the telomere region and regulate the length of telomeres by negatively controlling telomerase activity (Azzalin et al. 2007, Ng et al. 2009). Cells with active telomerase show a high level of TERRA promoter methylation, in contrast to those where the presence of this enzyme is not detected (Ng et al. 2009). This is probably because TERRA telomere repeats are complementary to the RNA template of telomerase and it is inhibited by competitive base pairing (Bisoffi et al. 1998). TERRA transcripts are involved in the formation of heterochromatin at chromosome ends interacting with the HP1 proteins and H3K9me3, as well as with HMTase Suv39H1 or Polycomb Repressive Complex 2 (PRC2) (Montero et al. 2018).

The interaction of TERRA transcript with TRF1 and TRF2 proteins can facilitate the binding of TERRA to the ends of chromosomes. Due to the fact that TRF1 and TRF2 can interact with chromosomes also in different regions (especially with ITR) (Simonet et al. 2011), TERRA transcripts can also bind non-telomeric sites (Cusanelli et al. 2013). TERRA, therefore, can regulate the expression of many genes (Chu et al. 2017). TERRA forms a complex with TRF2 and ORC1 (origin recognition complex 1), which facilitates DNA replication in telomeres (Deng et al. 2009). In addition, TERRA transcription itself, by the relaxation of chromatin, influences the initiation of DNA replication in this region during the S phase of the cell cycle (Bettin et al. 2019). It has been demonstrated that the expression level of TERRA depends on the phase of the cell cycle. It is high during the transition from the G1 to S phase, it is very high in the initial S phase, while it is reduced during the transition from the G2 phase to mitosis (Porro et al. 2010).

TERRA transcripts can promote homologous recombination between telomeres by creating RNA-DNA heteroduplex (R loops) at the ends of chromosomes (Chawla and Azzalin 2008). R loops can also block replication fork progression, cause double-strand breaks, delay cell aging and maintain genomic instability (Cusanelli and Chartrand 2015, Sollier and Cimprich 2015). For example, in the cells of the ICF syndrome, no methylation of the subtelomeric DNA was found, due to mutations in the DNMT3B gene. This results in a high level of the TERRA transcript, which forms telomeric R-loops, which in turn causes telomere dysfunctions (Cubiles et al. 2018). In addition, TERRA transcripts play a role in DNA damage response (DDR) caused by dysfunctional telomeres (Cusanelli and Chartrand 2015). Decrease in TERRA levels

resulting from either the action of siRNA (Deng et al. 2009) or ASO-LNA (antisense oligonucleotides – locked nucleic acid) (Chu et al. 2017) as well as their incorrect localization leads to many chromosome abnormalities. Depletion of TERRA transcripts activates DDR at the ends of the chromosomes, which leads to the formation of the "telomere dysfunction-induced foci" (TIF) (Lopez de Silanes et al. 2010). Hence, proper expression and localization of TERRA is required to maintain telomeres and chromosomal stability (reviewed in Bettin et al. 2019).

Histone substitution with their variants is another epigenetic mechanism that plays a role in the functioning of telomeres. In human and mouse cells, histone H3.3 variant was correlated with TERRA transcriptional repression in telomeres and subtelomeres (Law et al. 2010). Telomeric histone H3.3 variant is deposited through the ATRX (alpha thalassemia/mental retardation syndrome x-linked)-DAXX (death-domain associated protein) complex. The loss of the function of this complex results in the reduction of modifications characteristic of heterochromatin fractions in telomeric regions, also associated with lower H3.3 levels. It has the destabilizing effect through increased homologous recombination of telomeres, which facilitates ALT (Heaphy et al. 2011). MacroH2A1.2 histone variant involvement in ALT has also been demonstrated. MacroH2A1.2 is present in telomeres, especially in ALT cells, being a mediator of homologous recombination and response to replication stress (Kim et al. 2019). H2A.Z is another histone variant that occurs in telomeres. In *S. cerevisiae* H2A.Z variants hinder the spread of the heterochromatin (Grunstein and Gasser 2013). A strong anticorrelation was found between this histone variant deposition and DNA methylation (Zilberman et al. 2008, Kobor and Lorincz 2009). Higher levels of the histone H2A.Z variant were observed in *A. thaliana* mutants with reduced DNA methylation. Thus, it can be pointed out that H2A.Z deposition somehow protects the genome against DNA methylation (Zilberman et al. 2008). The study of the *Trypanosoma brucei* (Plimmer and Bradford, 1899) chromatin showed the presence of the H3V (histone H3 variant) protein in the telomeres. It has been found that H3V has several features common to CenH3, however, its absence does not disrupt chromosomal segregation (Lowell and Cross 2004). Another example of the histone variant is sperm-specific spH2B. This variant of H2B forms a specific complex with DNA *in vitro*, which may indicate its role in the recognition of telomeric DNA. It is also believed that this protein may be involved in the attachment of telomeres to the nuclear envelope (Gineitis et al. 2000).

Conclusions

Centromeres and telomeres are indispensable elements of every functional chromosome in Eukaryota. Considering the conservative role, their structure should be similar, not only in the context of the DNA nucleotide sequence, but also at the level of chromatin organization. Whereas in the case of telomeres this can be seen, in centromeres the similarity is observed mainly at the level of epigenetic modifications, with

a great diversity of nucleotide sequences. Although microscopic analysis indicates that they are heterochromatin elements, they should now be considered as specific regions of the so-called intermediate heterochromatin, i.e. having epigenetic features of both euchromatin and heterochromatin. Undoubtedly, epigenetic status plays an extremely important role in regulating both telomeres and centromeres. For it is the specific structure of chromatin, and not just the DNA sequence itself, that ensures the proper functioning of these regions during the entire cell cycle. Many analyses have been carried out, the results of which were often contradictory, hindering an unambiguous determination of epigenetic markers of centromeric and telomeric regions.

However, these analyses have allowed us to perceive the epigenetic nature of telomeres and centromeres as very complex systems, precisely regulated at many levels. Disorders of this regulation can lead to destabilization of the entire genome. It also turned out that adjacent regions, i.e. subtelomeres and pericentromeres, often no less important than key elements, were thought for a long time to be heterochromatin boundary areas. Currently, it seems that maintaining their epigenetic status affects the structure and functioning of telomeres and centromeres. There is a need for further research on other species that will allow better understanding of telomere and centromere regulation systems in all their complexity.

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